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Dental care for cancer patients undergoing radiotherapy of the head and neck region

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Abstract

Despite the considerable progress that has been made in radiotherapy in recent years, the side effects of ionising radiation treatment still constitute a major therapeutic problem on account of the multi-sidedness of the complications involved. The objective of the study was to determine the clinical condition of patients and the presence of fungi in the patients before, during and after radiotherapy, and on this basis prepare guidelines for local dental treatment as a recommended procedure for supporting cancer treatment. A total of 82 patients were treated for cancers of the head and neck organs with radiotherapy. The clinical condition of the oral cavity was assessed as was the appearance of fungi (a qualitative and quantitative assessment) in patients prior to the beginning of treatment, during treatment (weeks 2 and 4 of treatment), as well as after its conclusion. The sensitivity of selected strains of fungi to anti-fungal drugs was also assessed using the ATB Fungus method. During the course of the radiotherapy the condition of patients deteriorated significantly, especially in week 4 of the treatment, which was confirmed by mycological tests and the appearance of symptoms of *oral mucositis*. Assessments of fungal abundance (intensiveness) of fungi at particular stages of the study illustrates the dynamic of the fungal process. Results: 1) the use of radiotherapy has side effects which have a negative impact on the oral capacity of patients, i.e. inflammation of the mucous membrane (*oral mucositis*) and the appearance of erosion and ulceration; 2) simultaneously, the level of yeast-like fungi increases and candidiasis develops; 3) bacterial and fungal infections, as well as increasing acute post-radiation reaction in the mucous membranes of head and neck organs, requires prophylaxis and dental treatment.

Key words

radiotherapy, oral cavity, candidiasis, cancer patients, dental care

INTRODUCTION

Urbanisation, a longer life expectancy and specific lifestyle factors (habits and addictions) have led to an increase in the number of patients suffering from cancer. Each year, 11 million people worldwide are diagnosed with malignant tumours, almost 7 million of whom die as a result (epidemiological data from WHO, EU, NCI from 2005). Some 120,000 new cases of the disease are reported in Poland each year, of which 85,000 are terminal. According to the European Society for Medical Oncology, in Poland malignant tumours of the oral cavity and the throat account for 6% of all cancer patients each year, and the five-year survival rate is 23.3% for men and approximately 40% for women [1].

Alongside surgery, radiotherapy is one of the traditional methods used to treat malignant tumours of the head and neck, and according to estimates is administered in various forms in around 50% of patients. Radiotherapy plays an important role in the treatment of patients with cancers in this region of the body since its effectiveness is comparable with surgical treatment, and, moreover, it makes it possible to save the organ affected by the cancer, thereby preventing the patient from suffering permanent mutilation.

The main issue of importance during radiotherapy of cancers of the head and neck are lesions resulting from acute radiation damage, i.e. inflammation of the mucous membrane, otherwise known as *oral mucositis* [2, 3]. A number of factors have a major effect on the development and intensification of *oral mucositis,* including the type of radiation administered, the way the dose is fractionated, and the cumulative dosage. Severe post-radiation oral mucositis occurs in all patients with cancers in this region who have undergone conventional radiation treatment, i.e. a dose of 60-70 Gy administered in 30-35 fractions over a period of 6-7 weeks. This leads to the onset of secondary infections (mainly fungal) often accompanied by pain, which can prevent the consumption of solids and liquids. Some patients then even require a dosage of narcotic pain killers. The most intense pain appears in areas of non-attached, non-keratinised mucous membrane – in the cheeks, soft palate, mucous part of the lips, and floor of the mouth [4, 5].

During the course of radiotherapy, damage to the oral mucous membrane is caused by fungal growth, most commonly in the form of *Candida* [6, 7, 8]. The principal local factors predisposing a patient to the onset of mycosis are the following: poor oral hygiene, diminished salivary secretion, the wearing of extensive dentures and long-term inflammation of the mucous membrane. The onset of candidiasis in the oral cavity during radiotherapy is usually acute in character. The fungi can colonise other sections of the alimentary canal, thereby causing inflammation of the oesophagus, diarrhea, and also general infection [9, 10]. One of the most serious side-effects of radiotherapy is xerostomia, which can last for up to many years [11, 12].

Despite the considerable progress made in radiotherapy in recent years, the side-effects of such treatment still constitute

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a major therapeutic problem on account of the many-faceted complications. Studies in this area have been conducted not only by oncologists and specialists in cancer radiotherapy, but also by geneticists, microbiologists, and recently also by dentists.

OBJECTIVE OF THE STUDY

The objective of the study was to determine the clinical state and microflora (qualitative and quantitative analysis of the fungi) of the oral mucous membrane in patients with cancer of the organs of the the head and neck prior to the commencement of radiotherapy, during the course of such treatment (at weeks 2 and 4 of treatment), as well as 4-6 weeks after the termination of the radiotherapy, and on this basis prepare guidelines for local dental treatment as a recommended procedure supporting cancer treatment.

MATERIAL AND METHODS

The study method comprised both a clinical part and a laboratory part, including microbiological (mycological) tests. The cycle covered the following:
- a clinical assessment of the oral mucous membrane in patients with cancers of the organs of the head and neck (prior to radiation, during the course of radiation – during the second and fourth week of treatment, and after termination of the treatment);
- determining the frequency of fungal infections, identifying isolated fungi and providing a quantitative assessment of the abundance of fungal growth (quantitative tests);
- an assessment of the sensitivity of isolated fungi to anti-fungal drugs;
- establishing a schema for local treatment (depending on the clinical condition and state of the oral microflora), and administering this treatment to patients both during and after termination of the radiotherapy.

A total of 82 patients took part in the study, aged between 27-81 (average age 58.6±10.7), consisting of 63 men (76.8%) aged 27-81 and 19 women (23.2%) aged 35-76, who were being treated for cancer of the organs of the head and neck, and who underwent primary radiation or post-operative radiation at the M. Skłodowska-Curie Memorial Institute of Oncology in Krakow. Patients received a radiation dose of 60-70 Gy administered in 30-35 fractions over a period of 6-8 weeks.

The most common forms of cancer were cancer of the larynx, which was diagnosed in 43.9% of the patients (36 patients), cancer of the tonsils, identified in 15.85% of cases (13 patients), and nasopharyngeal cancer, which was discovered in 7 patients (Fig. 1).

From the total group of 82 patients, 31 who underwent radiotherapy (37.8%) came from the countryside, 35 (42.7%) were residents mainly of small towns with populations of up to 30,000, while 7.3% of the patients (6 persons) lived in large cities (Fig. 2).

Of the 82 patients in the study, 90.2% (74 persons) were regular smokers (23 of whom had smoked more than 20 cigarettes a day for more than 30-40 years), and 9.8% were non-smokers (8 patients).

27 of the patients drank alcohol excessively (32.9% of the respondents). Another 31 patients (37.8%) had had

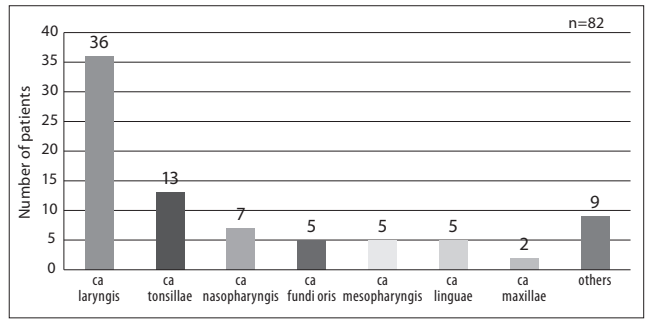


Figure 1. Types of malignant neoplasms

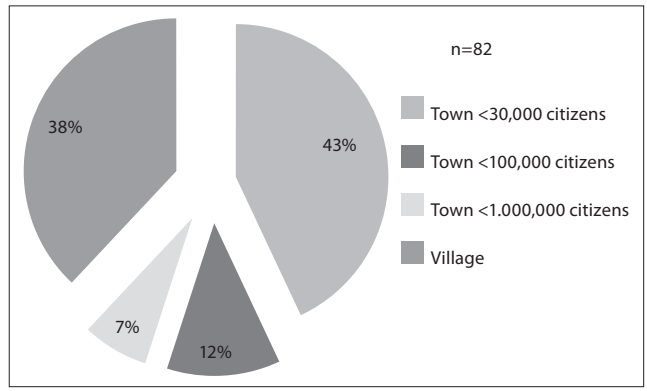


Figure 2. Classification of patients based on city size

contact with harmful substances in the workplace (paints, glues, varnishes, etc.), while 50 persons reported suffering from high or moderate levels of stress (61% of the patients). 47 of the patients (31%) had earlier undergone surgery with radiotherapy used as supportive therapy. The only treatment received by the other patients (35 persons) was ionising radiation.

All patients had both an interview and a physical examination, which included a clinical assessment of the state of the oral cavity, the cancer treatment being administered, the results of laboratory tests and the treatment being received.

The clinical examination covered the following cycle of tests:
- prior to radiotherapy (assessment of initial state);
- in the second week of radiotherapy (an assessment of the effects of radiotherapy on the state of the patient's oral cavity);
- implementation of dental treatment procedure;
- in the fourth week of radiotherapy and second week of dental treatment (an assessment of the effects of supportive dental treatment);
- continuation of dental treatment;
- final examination i.e. after the termination of the radiation treatment and the termination of the supportive dental treatment.

The intensity of lesions in the mucous membrane were assessed using the 5-point WHO scale:
0 – no symptoms of disease in the oral mucous membrane;
I – erythema of mucous membrane, swelling, soreness in oral cavity;
II – erythema of mucous membrane, swelling, surface erosion, patient can swallow solid foods;
III – erythema of mucous membrane, swelling, presence of ulceration, patient can only take liquid foods;

IV – erythema of mucous membrane, swelling, ulceration, patient fed parenterally.

Smears were taken of the mucous membrane of the right cheek together with washings from the oral cavity. The mucous membrane smear was taken using a sterile plastic wand with a viscose swab, which was applied to the mucosa in the established position and rotated 360°. The washing from the oral cavity was obtained after instructing the patients to rinse their oral cavities with 5 ml of physiological salt for 30 seconds. The material was collected in a sterile plastic container while observing the generally applied rules for microbiological tests regarding the time and method used to collect the biological material, the volume and amount of the samples taken and transported to the microbiological lab. The standard of care when working with potentially infectious materials was adhered to [13]. The collected clinical material was used to carry out mycological tests. To identify the fungi, the materials were cultured on a Sabouraud base. The amount of fungi was assessed in a 1 ml washing, and the profusion of fungi was assessed semi-quantitatively according to the following formula:

0 – no fungal growth

1 – slight growth (+): individual colonies (from 1-10 colonies);

2 – moderate growth (+ +): 11-30 colonies;

3 – abundant growth (+ + +): from 31-100 colonies;

4 – very abundant growth, confluent (+ + + +): above 100 colonies

All the isolated strains were identified according to the methodology applied in mycological diagnostics. The sensitivity of the fungi to anti-fungal drugs (5-Fluorocytosine (5FC), Amphotericin B (AMB), Fluconazole (FCA), Itraconazole (ITR) was assessed using the ATB Fungus 2 INT [14] test, while their sensitivity to nystatinum (NYS) was assessed using the disc-diffusion method. The patients were examined and clinical material taken prior to the beginning of radiotherapy, in the second week of radiotherapy, in the fourth week of treatment, and after the termination of the treatment (4-6 weeks).

The results of the clinical and laboratory tests were prepared statistically using the software *STATISTICA 7.1* and R [15]. When testing the hypotheses an error level of α=0.05 was adopted. The analysis included tests for non-parametric variables: the chi-squared test, a non-parametric variance of analysis (AOV) – the Friedman test for associated variables and a *post-hoc* analysis following the Friedman test.

RESULTS

For 47 of the 82 patients, radiotherapy constituted supplementary treatment for earlier performed surgery. Some of these patients reported subjective complications: a sensation of burning, tautness and dryness in the oral cavity. In the preliminary examination – prior to the commencement of radiotherapy – 16 patients (19.5%) reported a burning sensation in the oral cavity, and 12 (14.6%) reported tautness and dryness in the mucous membrane. In the second week of radiotherapy the number of patients reporting a burning sensation in the oral cavity had increased to 37 (45.1%), while the number reporting the same complications in the fourth week of treatment had risen further to 56 (68.3%). These

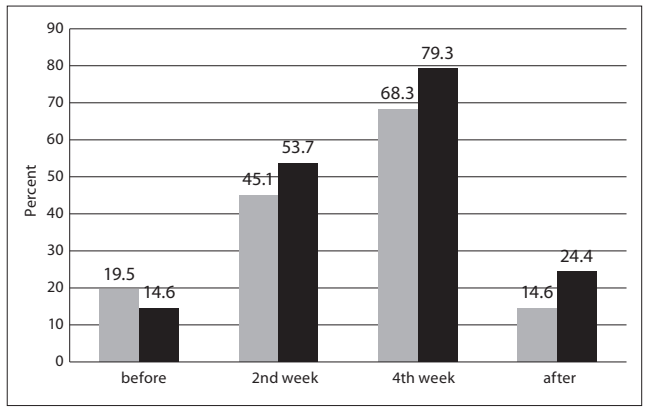


Figure 3. Percentage of patients reporting subjective ailments in the oral cavity in particular stages of the radiotherapy. The feeling of dryness and tension of mucous in oral cavity have been marked with gray colour; the feeling of burning – has been marked with the black colour

Table 1. Evaluation of oral mucous membrane according to five grade WHO scale

Oral mucosa evaluation (grade)	Number of patients and percentages		
	Before radiotherapy	In second week of treatment	In fourth week of treatment
0	70 (85.4%)	0 (0)	0 (0)
I	12 (14.6%)	17 (20.7%)	12 (14.6%)
II	0 (0)	45 (54.9%)	29 (35.4%)
III	0 (0)	20 (24.4%)	41 (50.0%)
IV	0 (0)	0 (0)	0 (0)

complications occurred regardless of the dental treatment the patients received. Similarly, the number of persons reporting tautness and dryness in the oral cavity also increased. In the second week of radiotherapy 44 people (53.7%) complained of this complication, and in the fourth week of treatment this number had risen to 65 patients (79.3%). An examination carried out 4 weeks after the termination of anti-cancer therapy showed that dryness of the mucous membrane was noted in 20 patients (24.4%) (Fig. 3).

The condition of the mucous membrane prior to commencement of radiotherapy and at week 2 and week 4 of radiotherapy is presented in table I. As the radiotherapy continued (week 4), the condition of the patients deteriorated significantly and in the majority of patients (85.4%) symptoms of *oral mucositis* were observed with accompanying erosions and ulcerations (levels II and III according to the WHO scale). Figures 4 and 5 show the clinical changes observed at week 4 of the radiotherapy.

A breakdown of fungal growth intensity noted prior to the commencement of the treatment, in the second and fourth week of treatment and after the termination of the treatment is show in Figure 6. Prior to the commencement of the radiotherapy, no fungi was cultivated in 44 patients (53.7%), while fungi in the form of *Candida* was assessed as slight (+) or moderate (++) in 34 persons (41.5%), and abundant growth (+++) was noted in 4 cases. In the second week of radiotherapy the number of patients in which no fungi was cultivated had declined to 27. On the other hand, the number of persons in whom abundant fungal growth was noted had risen from 4 to 20 (+++). In week 4 of radiotherapy, fungal growth had increased in intensity. Very abundant,

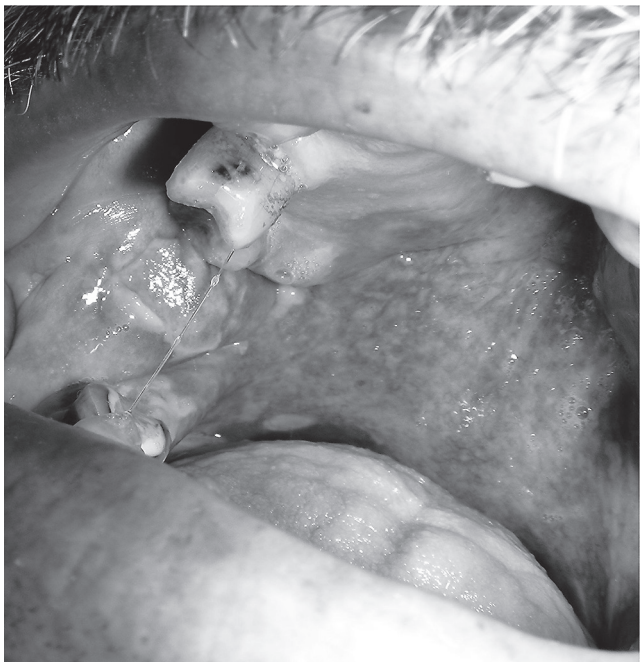


Figure 4. Fourth week of radiotherapy. Visualization of the lesions on palate and ulceration on the right buccal mucosa

Figure 5. Fourth week of radiotherapy. Visualization of ulcerations on the palate and leucoplakia on the left buccal mucosa. Typical mycotic lesions on the tongue (the presence of C*andida* strains confirmed in mycological examination)

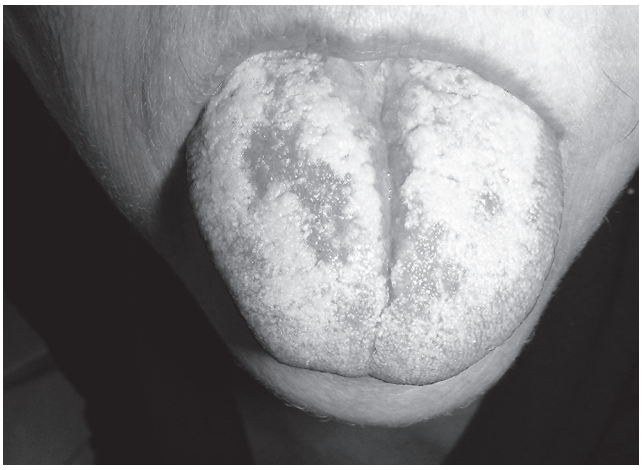


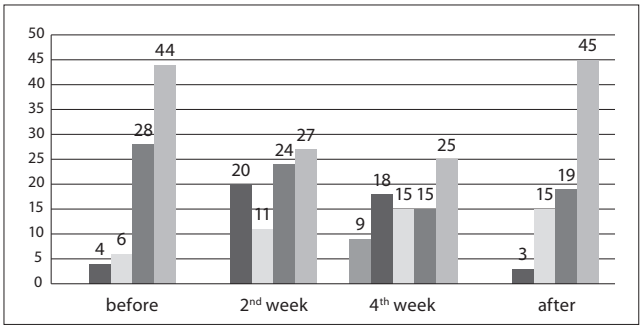
Figure 7. Fourth week of radiotherapy. Tongue candidiasis (the presence of C*andida* strains confirmed in mycological examination)

confluent fungal growth (++++), which had not been noted earlier in any of the patients in the study, was now observed in 9 persons (11%). Abundant fungal growth (+++) was observed in 18 persons (22%), and moderate growth (++) in another 15 (18.3%). However, the *post hoc* test following the Friedman analysis revealed no differences in fungal growth intensity between the second and fourth weeks of the radiotherapy.

The mycological test, carried out on patients following the termination of the ionising radiation treatment, showed no fungi cultivation in 54.9% of the patients. In addition, fungal growth intensity had returned to the same level observed prior to the beginning of the treatment (*post hoc* test after the Friedman analysis at a level of p=0.05). Abundant fungal growth (+++) was only noted in 3 persons, moderate fungal growth (++) was observed in 15 cases and slight growth (+) in another 19.

Figure 7 presents a clinical picture of candidiasis of the oral cavity at week 4 of radiotherapy, as confirmed by the mycological test (abundant growth- +++).

Table 2 shows the Minimal Inhibitory Concentration (MIC) values, determined using the ATB Fungus method, of the studied drugs (5-FC, AMB, FCA, ITR) for 84 strains of fungi isolated from patients at different stages of the treatment. 63 strains belonged to the species *C. albicans,* and 21 strains to the species *Candida* non-*albicans*. The Table presents the results of the MIC [mg/l] determination in the form of the mean, scope and modal value (most frequently appearing value) for particular species. Some strains were shown to be resistant to fluconazole and itraconazole.



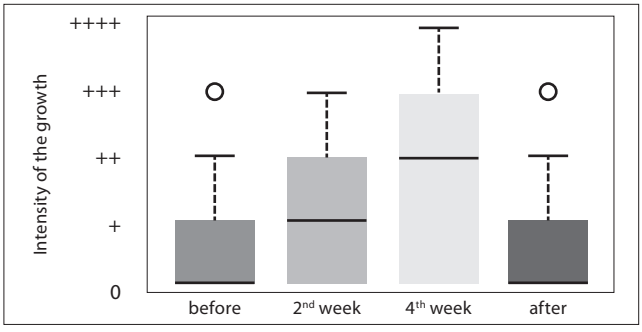


Figure 6. The change of the intensity of fungal growth during radiotherapy. On the boxplot chart the line shows median, box – quartile deviation, whiskers – the range of data, circles – outliers. (Only those patients, who had the growth of fungi at any stage of treatment stated, have been analysed). On the left side – the intensity of fungal growth in particular stages, shown by the percentage of the isolates in the given group

Table 2. MIC values of the drugs tested to 84 strains (mg/l)

Species	*n*	5-FC			AMB			FCA			ITR		
		Mn	R	Md	Mn	R	Md	Mn	R	Md	Mn	R	Md
C. albicans	63	0.5	-	0.5	0.5	-	0.5	44.2	0.25-128	128	2.1	0.125-4	4
C. glabrata	5	3.5	0.5-8	0.5	0.5	-	0.5	34.5	0.25-128	none	0.825	0.125-2	0.5
C. kefyr	3	0.5	-	0.5	0.5	-	0.5	0.42	0.25-0.5	0.5	0.125	-	0.125
C. krusei	4	2.7	2-4	2	0.5	-	0.5	13.3	8-16	16	0.375	0.125-0.5	0.25
C. lusitaniae	3	0.5	-	0.5	0.5	-	0.5	2.2	0.5-4	none	0.42	0.125-1	0.125
C. pseudotropicalis	1	0.5	-	0.5	0.5	-	0.5	0.25	-	0.25	0.25	-	0.25
C. tropicalis	5	0.5	-	0.5	0.5	-	0.5	68	8-128	none	3.25	1-4	4

MIC – minimal inhibitory concentration
5-FC – 5-fluorocytosine, AMB – amphotericin B, FCA – fluconazole, ITR – itraconazole
Mn – mean, R – range, Md – modal

The sensitivity of the 63 strains of *C. albicans* to 5 antifungal drugs (AMB, 5-FC, FCA, ITR and NYS) is assessed in Table 3. All strains turned out to be sensitive to amphotericin B and 5-fluorocytozine, while in the case of nystatinum, 62 strains were shown to be sensitive, and only 1 showed average sensitivity. On the other hand, 38 strains (60.3%) were shown to be resistant to itraconazole and 21 strains (33.3%) to fluconazole.

Table 3. The susceptibility of 63 *Candida albicans* strains

	AMB		5-FC		FCA		ITR		NYS	
S	63	100%	63	100%	39	61.9%	23	36.5%	62	98.4%
I	0	0%	0	0%	3	4.8%	2	3.2%	1	1.65
R	0	0%	0	0%	21	33.3%	38	60.3%	0	0%

S – sensitive, I – intermediate, R – resistant

DISCUSSION

The results of the presented study are in accordance with data from the literature on the onset and course of *oral mucositis* [16]. In the second week of radiotherapy, more than half of the patients (45 persons) suffered acute post-radiation mucosal reaction. A clinical examination confirmed swelling and reddening of the mucous membrane. Changes were also observed in the form of erosions, sometimes covered with a fibrous deposit. The patients complained of complications affecting the mucous membrane – a feeling of tautness and burning, pain brought on by the lesions and reduced saliva secretion. The above-dsescribed symptoms mainly occurred at night. The patients also reported taste disturbances. In week four of the radiation treatment, the condition of the patients deteriorated significantly, and in the majority of cases (70 persons) symptoms of acute post-radiation mucosal reaction (stages II and III according to the WHO scale) were observed. Increasing pain and xerostomia (reduced saliva secretion) not only impeded the consumption of solid foods but made actual eating impossible. Patients could only be fed in liquid or semi-liquid form.

The MIC values symptoms described above of *oral mucositis,* as well as the complications connected with it, are a consequence of the direct effects of ionising radiation, as well as of reduced saliva secretion and changes in the composition of the patient's saliva – a higher concentration of electrolytes, greater density, reduction in pH and a decline in the concentration of immunoglobulin type A. Also not without significance were the patient's hygiene habits. Some authors believe that the patient's failure to observe oral hygiene is caused by depression resulting from the diagnosis of cancer, as well as by additional pain and soreness originating from the mucous membrane [17, 18].

Similar observations were made and described by the authors Carl & Emrich [19], who examined 98 patients who had undergone radiotherapy for oral cancer, receiving a dose of more than 50 Gy during the course of the treatment. The patients in the study had second and third degree mucosal inflammation of the oral cavity (according to the three-degree scale used by the authors).

A study conducted by Grötz et al. [20], and confirmed by both Almståhl et al. and Thaweboon et al. [21, 22], shows that mycosis is a typical infection of the mucous membrane occurring during radiotherapy for head and neck cancers. Other authors observed that systemic disorders primarily brought on by cancer, radiation and antibiotic treatment create suitable conditions for the onset of oral candidiasis [23, 24, 25]. The Polish literature includes a number of studies that, just like the presented study, confirm the appearance of fungi, especially in the form of type C. *albicans,* in the oral cavity of cancer patients [26, 27]. A longitudinal study carried out in our centre comprising a period of around 2 months for every patient showed that *Candida albicans* fungus predominates at all stages of the study. In weeks 2 and 4 of radiotherapy the number of patients with oral fungi increased (at week 2-67.1%, and at week 4-69.5%). On the other hand, the number of patients with fungi present in the oral cavity prior to treatment was similar to the number with fungi after the treatment was completed (prior to radiotherapy: 38 persons – 46.3%, after termination of therapy: 37 persons – 45.1%).

The methods used to treat this group of patients (in particular radiotherapy and/or chemotherapy) disturb the proper functioning of the immune and haemopoietic systems, which has a negative effect on oral health. Fungal foci in the oral cavity can provide a source of further invasions, and as a consequence can cause multifocal candidiasis, as well as recurrent mycosis of other organs [28].

The presented study showed that a high percentage of strains are resistant to imidazole drugs (33.3% of strains were resistant to fluconazole, 60.3% of strains were resistant to itraconazole) while at the same time remaining sensitive to AMB, 5-FC and NYS. The increased resistance to drugs from the imidazole group is becoming an increasingly serious clinical problem because these drugs, due to their

pharmacodynamics and limited undesired effects, are popular among doctors and widely recommended. In particular, the long-term administration of fluconazole can lead to higher induced resistance. Other authors [29] have also observed the increasing resistance of strains of *Candida* fungi, in particular *Candida non-albicans,* to imidazole drugs. When fluconazole treatment is unsuccessful, nystatinum proved to be effective in the presented study, which has also been confirmed by studies on the sensitivity to this drug *in vitro.*

In turn, a comparative study on the sensitivity of fungi to fluconazole and voriconazole [30] covered 79 strains of *C. glabrata* isolated from the oral cavity of patients who had earlier undergone radiotherapy for cancer of the head and neck. The sensitivity of these strains to the above 2 drugs was assessed using the quantitative method NCCLS M27-A2. The study showed that both drugs had high MIC values, including a higher MIC value for voriconazole, and the MIC value for fluconazole was even higher.

The condition of the oral mucous membrane not only depends on the total dose of radiation administered, but also on the state of the patient's dentition and mucous membrane prior to the beginning of the treatment. It is extremely important that every patient referred for radiotherapy has undergone a full, radical hygienisation of the oral cavity with the aim of eliminating potential infection foci. Treatment of oral complications resulting from ongoing or completed ionising radiation should be planned and organised for each patient individually.

A number of foreign studies have focused on the issue of dental care and the problem of properly preparing the patient for radiotherapy. Our own observations show that many patients begin radiation treatment without undergoing any oral rehabilitation or hygienisation procedures. As earlier results have confirmed, this intensifies the side-effects, which in turn significantly increases the pain experienced by these patients.

Based on an analysis of the results of studies conducted with the framework of the presented paper, the author proposes an algorithm for supportive dental treatment for patients undergoing radiotherapy for cancers of the head and neck region, which would be divided into the following tasks:

Period I – prior to the commencement of radiotherapy:
- oncological-dental consultation;
- elimination of potentially active dentogenic infection foci;
- removal of active and secondary caries foci, as well as the placement of dental fillings;
- performance of professional hygienisation procedures;
- instructions in oral hygiene to be observed by the patient;
- elimination of trauma factors affecting the periodontium and soft tissue in the oral cavity, as well as prosthetic restorations;
- recommendations for correct diet.

Period II – during radiotherapy:
- further co-operation between dentist and oncologist;
- application of preparations designed to moderate the effects of *oral mucositis*;
- treatment of local lesions in the oral mucous membrane through the application of mycological treatment and/or anti-bacterial treatment;
- elimination or moderation of xerostomia symptoms;
- motivating patient to observe oral hygiene.

Period III – following the termination of radiotherapy:
- continuation of collaboration with patient;
- motivating patient to maintain proper oral hygiene;
- elimination of existing side-effects of ionising radiation treatment (xerostomia, candidiasis, bacterial infections) through the continuation of the targeted therapy.

CONCLUSIONS

1. The use of radiotherapy has side-effects which have a negative impact on the oral cavity of patients, i.e. inflammation of the mucous membrane (*oral mucositis*) and the occurrence of erosion or ulceration.
2. Simultaneously, the level of yeast-like fungi increases and candidiasis develops.
3. Bacterial and fungal infections, as well as increasing acute post-radiation fungal reaction in the mucous membranes of the head and neck organs, require prophylaxis and dental treatment.

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